## REMARKS

### I. Status of the Claims

Claims 1-20 were originally filed. Claims 21-29 were later added. Upon entry of the present amendment, claims 1 and 20 recite that the taste cell specific G-protein beta polypeptide comprises the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5. Claims 2, 21, and 22 are canceled. No new matter is introduced. Claims 1, 3-20, and 23-29 remain pending.

### II. Claim Rejection

A. 35 U.S.C. §112, First Paragraph

Claims 1-29 were rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate enablement. Specifically, the Examiner stated that the specification is enabling for a method for identifying a compound capable of modulating signal transduction in taste cells by contacting the compound with a taste cell specific G-protein beta polypeptide comprising the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5, but is not enabling for a method for identifying a compound capable of modulating signal transduction in taste cells by contacting the compound with a taste cell specific G-protein beta polypeptide comprising an amino acid sequence more than 70% identical to SEQ ID NO:3 or SEQ ID NO:5. As amended, the pending claims recite the use of a taste cell specific G-protein beta polypeptide comprising SEQ ID NO:3 or SEQ ID NO:5. Applicants thus submit that the enablement rejection is overcome.

B. 35 U.S.C. §103

The Examiner maintained the rejection of claims 1-29 under 35 U.S.C. §103(a) for alleged obviousness over Margolskee *et al.*, Bruch *et al.*, Levine *et al.* or Ray *et al.*, and Negulescu *et al.* Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: first, the prior art references must teach or suggest all the claim limitations; second, there must be some suggestion or motivation, either in the references or in the knowledge generally available

to one of ordinary skill in the art, to combine the limitations; third, there must be a reasonable expectation of success in combining the limitations. MPEP §2143.

*Claim Limitations and Characterization of References*

Among all pending claims, claims 1 and 20 are independent claims. Claim 1 is drawn to a method for identifying a compound that modulates taste signaling in taste cells. The method comprises two steps: (i) contacting the compound with a taste cell specific G-protein beta polypeptide, which comprises the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5; and (ii) determining the functional effect of the compound upon the polypeptide. Claim 20 is also drawn to a method for identifying a compound that modulates taste signaling in taste cells. The method comprises four steps: (i) expressing a taste cell specific G-protein beta polypeptide in a host cell, wherein the G-protein beta polypeptide comprises the amino acid sequence of SEQ ID NO:3 or SEQ ID NO:5; (ii) expressing a promiscuous G-protein alpha polypeptide and a taste cell specific G-protein coupled receptor in the host cell; (iii) contacting the host cell with the compound that modulates taste signaling in taste; and (iv) determining changes in intracellular calcium levels in the host cell, thereby identifying the compound that modulates taste signaling in taste cells.

As previously characterized, Margolskee discloses Gustducin, a G-protein alpha subunit specifically expressed in taste cells. Margolskee also teaches generally that taste-modulating compounds may be identified using assays for taste cell specific proteins involved in taste transduction, such as Gustducin. ***Margolskee does not disclose the taste cell specific G-protein beta subunits of the present invention, e.g., SEQ ID NO:3 or SEQ ID NO:5.***

Bruch teaches that a common G-protein beta subunit is involved in the signal transduction of taste cells. ***Bruch does not disclose the amino acid sequence of the G-protein beta subunit.***

Ray and Levine disclose two G-protein beta subunits that are 100% identical to SEQ ID NO:3 and 97% identical to SEQ ID NO:5, respectively. The polypeptide of Ray was cloned from a heart cDNA library, and expression of the mRNA encoding the G-protein beta

subunit was shown in heart and brain. The polypeptide of Levine was cloned from a retina cDNA library, and expression was shown in four different cell lines: rhabdomyosarcoma, pheochromocytoma, neuroblastoma, and dermal fibroblasts. ***Neither Ray nor Levine discloses that the G-protein beta subunits are expressed in taste cells of the tongue.***

Negulescu discloses generally the use of promiscuous G-protein alpha subunits for identifying G-proteins, their ligands, and compounds capable of modulating signal transduction. ***Negulscu does not specifically relate to the use of promiscuous G-protein in the method claimed in the present application.***

*Bruch Does Not Inherently Disclose SEQ ID NO:3 or SEQ ID NO:5*

In characterizing Bruch, the Examiner took the position that even though this reference does not provide the amino acid sequence of the G-protein beta subunit found in taste cells, such amino acid sequence is inherent to the beta subunit and is therefore identical or gerater than 70% identical to that of SEQ ID NO:3 or SEQ ID NO:5 (page 8, lines 12-15, of the Office Action mailed May 20, 2004).

The Examiner's reasoning appears to be based on the assumption that there is only one G-protein $\beta$ subunit involved in taste signal transduction (the paragraph bridging pages 11 and 12 of the May 20, 2004, Action). Applicants respectfully disagree. As a quick search in the GenBank database for human G-protein beta subunits reveals multiple different amino acid sequences (*see, e.g.*, GenBank Accession Nos. NP_002065, NP_005264, NP_002066, NP_067642, NP_006569, NP_057278, P16520, RGHUB3, AAF04308, AAA52582, AAA35922, attached as Exhibit A), these amino acid sequences are not identical or even necessarily having a high percentage sequence identity. For instance, the alignment between SEQ ID NO:5 of the present invention (corresponding to GenBank Accession No. AAA52582) and GenBank Accession No. NP_057278 indicates a 45.3% sequence identity (attached as Exhibit B). These various human G-protein beta subunits are known to be expressed in a variety of tissues, including brain, pancreas, heart, kidney, placenta, liver, lung, and skeletal muscle (*see, e.g.*, Table 5 of Downes and Gautam, *Genomics* **62**:544-552 (1999) and page 290 of Jones *et al.*, *Biochem. Biophys. Acta* **1402**:288-291 (1998), attached as Exhibits C and D, respectively).

To rely on the inherency theory, the Examiner must demonstrate that an alleged inherent feature is a consistent, necessary, and inevitable occurrence and not a mere possibility or probability. According to the Federal Circuit, "[i]nherency ..... may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Continental Can Co. v. Monsanto Co.*, 948 USPQ2d 1746, 1749 (Fed. Cir. 1991). In the present case, the Examiner has not shown that the G-protein beta subunit in taste cells observed by Bruch *et al.* is necessarily identical to one having the amino acid sequence of SEQ ID NO:3 or 5 and not any other G-protein beta subunits. In light of the fact that there exist many different G-protein beta subunits, the identity of Bruch's G-protein beta subunit is uncertain and the Examiner's assertion that this polypeptide necessarily has the amino acid sequence as set forth in SEQ ID NO:3 or 5 is unsubstantiated without further evidence.

*Motivation to Combine the Claim Limitations*

In considering the above cited references, the Examiner has not identified a motivation or suggestion in the references for one of skill in the art to combine the claim limitations.

The Examiner pointed out that Margolskee teaches the mechanism of signal transduction involving G-proteins, which have $\alpha$, $\beta$, and $\gamma$ subunits, in olfactory, visual, hormonal, and neurotransmitter systems, discusses the need to develop a new assay system for testing tastants for their capability to modulate signal transduction in taste cells, and proposes several methods for such screening process. Applicants contend, however, the teaching by Margolskee *et al.* merely reflects the state of art and a general desire for new screening methods for identifying compounds capable of modulating signal transduction. This teaching at best provides a general motivation for one of skill in the art ***to try*** to establish a method for identifying taste modulating compounds using a G-protein $\beta$ subunit. It does not provide a specific motivation for an artisan to use the G-protein $\beta$ subunit comprising SEQ ID NO:3 or SEQ ID NO:5 in such a screening method. It is well settled that "obvious to try" is not the proper standard for obviousness. *See, e.g., N.V. Akzo v. E.I. du Pont de Nemours & Co.*, 1 USPQ2d 1704, 1707 (Fed. Cir. 1987); *in re O'Farrell*, 7 USPQ2d 1673, 1680-1681 (Fed. Cir.

1988). The Margolskee reference thus does not provide a specific motivation to combine the claim limitations.

Similarly, the Examiner has not idnetified any motivation or suggestion in the references by Bruch *et al.*, Levine *et al.*, Ray *et al.*, and Negulescu *et al.* for one of skill in the art to combine the claim limitations. Applicants submit that the cited references merely provide pieces of information that cannot be connected even when viewed in the hind sight, particularly because the identity of the G-protein beta subunit described by Bruch *et al.* remains a question.

*Reasonable Expectation of Success*

Furthermore, even if a specific motivation or suggestion to combine the claim limitations were established, there still would be no reasonable expectation of success in making such a combination.

Because of the number and diversity of G-proteins and G-protein subunits (*see, e.g.*, Downes and Gautam, *Genomics* **62**:544-552 (1999), attached as Exhibit C), there simply can be no reasonable expectation of success, without the benefit of extensive experimentation, when one attempts to use a particular G-protein subunit that has not been tested previously in a method taught by Margolskee in an effort to identify compounds capable of modulating taste signaling.

*Summary*

Though the limitations of the pending claims can be found in the cited references, the Examiner has not identified a motivation to combine the limitations or demonstrated a reasonable expectation of success in making the combination. This is particularly because the G-protein beta subunit reported by Bruch *et al.* has not been shown to necessarily comprise the amino acid sequence of SEQ ID NO:3 or 5.

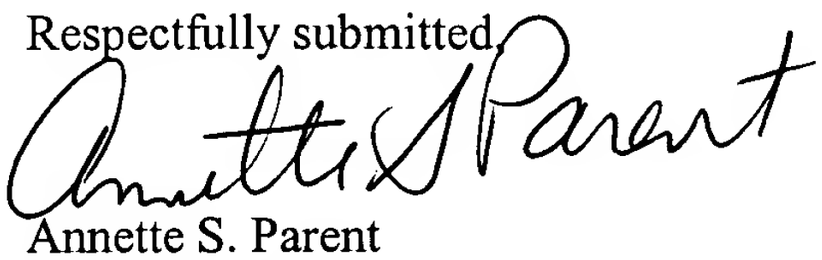
Applicants thus submit that no *prima facie* obviousness has been established and respectfully request the withdrawal of this rejection.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachments (Exhibit A: printouts of GenBank entries for amino acid sequences of G protein beta subunits; Exhibit B: sequence comparison between GenBank Accession Nos. AAA52582 and NP_057278; Exhibit C: Downes and Gautam, *Genomics* **62**:544-552 (1999); Exhibit D: Jones *et al.*, *Biochem. Biophys. Acta* **1402**:288-291 (1998))

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